

Remarks

The August 10, 2005 Official Action and the references cited therein have been carefully reviewed. In view of the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory response period of three (3) months was set in the August 10, 2005 Official Action. Therefore, the initial due date for response was November 10, 2005. A petition for a three (3) month extension of the response period is presented with this response, which is being filed within the three month extension period.

This is the **sixth** Official Action on the merits in this application and in all six Official Actions, the Examiner has raised new grounds of rejection, many of which were **not** in response to any amendments set forth by the Applicants. For example, Applicants note that claims 1-3, 7-11, 13-17, 20-22, 25-27, 29, 30, 32-38, 41, 42, and 47-49 were found to be in condition for allowance in the November 17, 2004 Official Action and the lone rejections of claims 4-6 and 31 were overcome by Applicants' amendments to the claims as indicated by the Examiner in the instant Official Action. However, the Examiner has rejected all of the pending claims raising two new grounds of rejection. Furthermore, Applicants note that claims 25-27, 30, 48, and 49 have been in condition for allowance since May 23, 2003 and that claims 1-11, 13-17, 20-22, 25-27, 29-32, 37, 38, and 47-49 had been in condition for allowance since November 20, 2003. To raise new grounds of rejection this late in prosecution on claims that have been previously found allowable in multiple Official Actions over the course of 2.5 years is unfair to Applicants and forces them to incur unnecessary costs in the prosecution of the instant application.

At page 2 of the Official Action, the Examiner has rejected claims 1-11, 13-17, 20-22, 25-27, 29, 30, 33-38, 41, 42, and 47-49 for allegedly failing to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

Claims 25-27, 29, 30, 48, and 49 have also been rejected under 35 U.S.C. §102(b) as allegedly anticipated by Dinsmore et al. (Theriogenology (1998) 19:145-151).

The foregoing rejections constitute all of the grounds set forth in the August 10, 2005 Official Action for refusing the present application.

In accordance with the instant amendment, Applicants have amended claims 1, 20, 33, 35, 37, and 47 to indicate that the media **optionally** comprises leukemia inhibitory factor (LIF). Support for these amendments can be found throughout the specification including, for example, at page 3, line 25 through page 7, line 29 and in original claims 1 and 12 wherein original claim 1 does not require the serum-free media to contain LIF and claim 12 requires the media to contain LIF. The above cited passage and original claim 12 also provide support for newly added claims 51-55. Support for new claims 56-59 can be found throughout the specification including, for example, in original claims 26 and 27 and Figure 2B and at page 30, lines 9-14 and page 48, lines 1-4.

No new matter has been introduced into this application by reason of any of the amendments presented herewith.

In view of the reasons set forth in this response, Applicants respectfully submit that the 35 U.S.C. §112, first paragraph rejection of claims 1-11, 13-17, 20-22, 25-27, 29, 30, 33-38, 41, 42, and 47-49 and the 35 U.S.C. §102(b) rejection of claims 25-27, 29, 30, 48, and 49, as set forth in the August 10, 2005 Official Action, cannot be maintained. These grounds of rejection are, therefore, respectfully traversed.

**CLAIMS 1-11, 13-17, 20-22, 25-27, 29, 30, 33-38, 41, 42, AND  
47-49 FULLY SATISFY THE ENABLEMENT REQUIREMENT OF 35 U.S.C.**

**§112, FIRST PARAGRAPH**

The Examiner has rejected claims 1-11, 13-17, 20-22, 25-27, 29, 30, 33-38, 41, 42, and 47-49 for allegedly failing to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. Specifically, it is the Examiner's position that while the specification is "enabling for a mouse primitive neural stem cell and a method of making and using a primitive neural stem cell ... produced from a culture of mouse ES cells," the specification allegedly fails to fully enable "a neural stem cell, method of making or method of using neural stem cell wherein the cell is produced from any species of ES cell other than mouse." The Examiner has applied the enablement factors provided at §2164.01(a) of the MPEP and concluded that, in view of the allegedly undeveloped and unpredictable state of the art and the alleged absence of guidance with regard to ES cells other than mouse ES cells, a skilled artisan would have to perform undue experimentation to practice the full scope of the claimed invention.

Applicants respectfully disagree with the Examiner's position. In In re Wands, 8 USPQ2d 1400 (1988), the Federal Circuit Court of Appeals held that engaging in experimentation to practice a claimed invention does not render the disclosure non-enabling as long as the experimentation required is not "undue". The Court stated that: "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" In re Wands, 8 USPQ2d 1400, 1404 (1988).

Applicants contend that the instant specification discloses the preferred culture conditions to generate primitive neural stem cells. Exemplary culture conditions for generating neural stem cells are disclosed throughout the specification (see, e.g., the Examples) and Applicants contend that a skilled artisan could effectively apply these methods and culture conditions to ES cells of other species. Any experimentation required, if at all, for inducing successful differentiation is standard in the art and cannot be considered undue.

However, to further demonstrate that the methods and culture conditions of the instant application are applicable to ES cells of species other than mice, Applicants have demonstrated that human embryonic stem cells can be plated and cultured in minimal, serum-free media such that clonal sphere colonies (i.e., neurospheres) are formed. These clonal sphere colonies comprise primitive neural stem cells and can be differentiated into neurons and glial cells.

Applicants intend to submit a Declaration pursuant to 37 CFR §1.132 to formally make this evidence of record at the USPTO. The signed Declaration will be forwarded to the USPTO immediately upon receipt of the same in the offices of the undersigned.

In light of all of the foregoing, Applicants submit that the rejection of the claims under §112 first paragraph for inadequate enablement is untenable and should be withdrawn.

**CLAIMS 25-27, 29, 30, 48, AND 49 ARE NOT ANTICIPATED BY  
DINSMORE ET AL.**

The Examiner has rejected claims 25-27, 29, 30, 48, and 49 under 35 U.S.C. §102(b) as allegedly anticipated by Dinsmore et al. Dinsmore et al. allegedly disclose a mouse ES cell line that can be induced into neural cells. Inasmuch as

the instant specification at pages 3-4 states that the instant invention describes "a previously unidentified primitive neural stem cell stage in the neural lineage, which defines the transition between ES cell and neural stem cell," it is the Examiner's position that the skilled artisan would conclude the ES cell culture in Dinsmore et al. would "comprise isolated primitive neural stem cells, which ... would express the various markers recited in the claims."

Applicants respectfully disagree with the Examiner's position. At the outset, Applicants respectfully submit that the Examiner has set forth an improper inherency rejection under 35 U.S.C. §102(b). The MPEP at §2112 states that:

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)

At page 8 of the instant Official Action, the Examiner concludes that because primitive neural stem cells are an "intermediate between stem cells and neural stem cells," there must be isolated neural primitive neural stem cells in "the ES cell cultures of Dinsmore et al." This is incorrect. As indicated hereinbelow, Dinsmore et al. employed media containing serum for differentiating the ES cells whereas the instant invention differentiated ES cells with serum-free media. Inasmuch as the ES cells of Dinsmore et al. were exposed to a myriad of different known and unknown factors present in serum, the ES cells of Dinsmore et al. likely differentiated in a completely different manner than the ES cells of the instant invention. Indeed, the ES cells of Dinsmore et al. may have bypassed the primitive neural stem cell stage and directly differentiated from ES cells into neurons. Since the cultures of Dinsmore et al. may never have contained primitive neural stem cells at any point, the

"allegedly inherent characteristic" that primitive neuron stem cells are present does not "necessarily flow" from the teachings of Dinsmore et al. Accordingly, Applicants submit that the Examiner has failed to set forth a proper rejection under 35 U.S.C. §102(b).

Furthermore, Applicants submit that the Examiner has failed to provide evidence that **isolated** primitive neural stem cells are taught by Dinsmore et al. Indeed, the Examiner states that the "ES cell cultures of Dinsmore et al. comprise isolated primitive neural stem cells." However, Applicants submit that the alleged transient presence of primitive neural stem cells in a culture does not satisfy the requirements of being "isolated."

Additionally, Applicants note that the ES cells of Dinsmore et al. were cultured according to standard methods used in the field. Specifically, undifferentiated ES cells were maintained in an undifferentiated state by culturing in media comprising 10% horse serum and other factors such as LIF (page 146). Dinsmore et al. then demonstrate that their specialized media, which does not include LIF but does include 10% fetal calf serum, retinoic acid, thyroxine, hydrocortisone, somatostatin and bovine pituitary extract (which is uncharacterized), causes ES cells to differentiate into "neuronal" cells with absolutely no mention of a neural stem or progenitor cell characteristics. The presence of uncharacterized molecules in the pituitary extract and the fetal calf serum indicates that their media conditions were entirely distinct from the media employed in the instant application and would have affected the ES cell differentiation differently from the instant conditions. Indeed, the instantly claimed methods for generating a primitive neural stem cell recite the use of a serum-free media, which is in direct contrast to the media employed by Dinsmore et al.

Furthermore, Dinsmore et al. state at page 148 that the "neuronal cells that resulted from RA induction were a near homogeneous population of cells that extended neurites ... [and] stained positive for the neurotransmitter  $\gamma$ -aminobutyric acid, glutamic acid decarboxylase, neurofilament, nerve-specific tubulin, and the neural surface antigen A2B5." A skilled artisan would appreciate, based on the expression of these markers, that this "near homogeneous" population of ES derived cells clearly represents neurons and **not** neural stem or progenitor cells.

Dinsmore et al. also explicitly state at page 148 that "these same cells failed to stain for glial-specific markers." The instantly claimed primitive neural cells, however, are multipotent. Notably, the instant specification teaches in Example 2 (page 30) that ES-derived sphere colonies comprise "both neuronal and glial lineages." The absence of glial-specific markers in the cells of Dinsmore et al. clearly indicates that they have isolated differentiated neurons and not multipotent primitive neural stem cells.

Given the vast differences in media used for ES cell differentiation and the clear evidence that the cells of Dinsmore et al. were terminally differentiated into neurons, it is clear that the ES cultures of Dinsmore et al. do not comprise primitive neural stem cells.

At page 8 of the Official Action, the Examiner also states that "the specification provides no explicit definition of a 'sphere colony'" and, therefore, contends that the cells that adhered to each other in the teachings of Dinsmore et al. are "viewed as meeting the limitations of a sphere colony comprising at least one primitive neural stem cell according to the limitations of claim 49." Applicants respectfully disagree. The instant specification clearly indicates that the spheres derived from the ES cells in the application are a result of the clonal proliferation of a single cell (see, e.g., page 15, lines 4-10 and page 30, lines 7-9). Clearly,

multiple cells adhering to each other to form an aggregate as in Dinsmore et al. is **not** equivalent to the clonal proliferation of a single cell into a sphere with multiple cells. Notably, primitive neural stem cells must be able to clonally proliferate to produce neurons **and** glial cells.

In light of all of the foregoing, Dinsmore et al. do not anticipate the isolation of primitive neural stem cells because the media conditions (including uncharacterized components such as serum) described in the reference appear to cause direct and terminal differentiation of ES cells, i.e., the methods described give rise to neurotransmitter expressing neurons with no evidence of clonal proliferation or self-renewal. Moreover, the reference clearly indicates that no glial cells are present.

In light of the foregoing, Applicants submit that the instant rejection under §102(b) is untenable and respectfully request its withdrawal.

#### **CONCLUSION**

In view of the amendments presented herewith and the foregoing remarks, it is respectfully urged that the rejections set forth in the August 10, 2005 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,  
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By



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